

### **Remarks**

Claims 1-65 and 124-134 are pending in the present application. Claims 66-123 were withdrawn by the Examiner from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention. Claims 1, 4, 12, 14, 15, 18-20, 23-30, 34, 36, 44, 45, 54-57, 65, 124, and 131 were rejected under 35 USC § 102(e), and Claims 2-3, 5-11, 13, 16-17, 21-22, 31-33, 35, 37-38, 46-47, 125-130, and 132-134 were rejected under 35 USC §103(a). Claims 39-43, 48-53, and 58-64 were objected to as being dependent upon a rejected base claim, but the Examiner noted that they would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims. Applicants respectfully request reconsideration of the application, withdrawal of all rejections, and allowance of the application in view of the amendments and remarks below.

### **The Amendments to the Claims**

In order to expedite prosecution and issuance of the application, Applicants have amended claims 39, 48, 49, 50, to incorporate all the limitations of the base claims and any intervening claims, as the Examiner has stated that these claims and the subsequent claims that depend from these claims, specifically claims 40-43, and 51-53, would be allowable if written in this manner. Likewise, Applicants have amended claims 58-59, to incorporate all the limitations of the base claims and any intervening claims, except for the limitation of heating "sequentially." Applicants believe that removal of this limitation is supported by the specification and that incorporating all other limitation as the Examiner stated would render these claims and the subsequent claims and 60-61 that depend from these claims allowable if written in this manner.

The amendments to the claims do not introduce new matter. Applicants respectfully submit that the amendments to the claims put the application in condition for allowance. The Examiner is respectfully requested to enter the amendments to the claims and allow all pending and amended claims.

### **Interview Summary**

In order to expedite prosecution, Applicants requested to Interview with Examiner Erez to obtain further clarity as to the rejections stated in the Office Action dated December 15, 2003. A summary of the interview is stated below.

On February 23, 2004, Dr. Elaine Stracker, attorney of record for Applicants, and Dr. Joshua Rabinowitz, V.P. of Research at Alexza, MDC contacted Examiner Erez via telephone. Dr. Stracker

noted that a specific claim limitation in all of the independent claims at issue in Applicants' invention was "mixing the resulting vapor with a gas, in a ratio, to form a desired particle size when a stable concentration of particles in the gas is reached." This claim limitation was notably absent from the Kessler reference (U.S. Patent No. 6,095,153) and therefore Dr. Stracker was confused as to the relevance of the Kessler reference as a 102 reference against the Applicants' claims. Examiner Erez stated that this feature of Applicants' invention has been inadvertently missed on his first review and that Kessler should likely have more properly been cited as a 103 reference against the claims. Examiner Erez stated that another review would be necessary and that the next Office Action would not be final if additional references were found. Dr. Stracker also noted that the Thwaites and Olsson references cited as 103 references were directed to vaporized gases and not aerosols. Additionally, Dr. Stracker noted that Wang (US 5,355,770) was directed to formation of plasmas. No other references or prior art was discussed. It was agreed that Dr. Stracker would respond to the first Office Action with regard to Kessler and could request reconsideration of the other references in light of Kessler not disclosing the limitation of "mixing the resulting vapor with a gas, in a ratio, to form a desired particle size when a stable concentration of particles in the gas is reached." Additionally, the Examiner requested that Applicants, in order to expedite prosecution, cite to support in the specification for this limitation in the response. Applicants agreed to provide this cite.

The information requested by the Examiner can be found in the instant application at paragraph [0066] (in the published version), which states "A desired particle size is achieved by mixing a compound in its vapor-state into a volume of a carrier gas, in a ratio such that when the number concentration of the mixture reaches approximately  $10^9$  particles/ml, a "stable" particle size is present. The amount of compound and the volume of gas are each predetermined to achieve this ratio." The desired particle sizes and "non-desirable" particle size are defined in paragraph [0017]. Additionally, information as to how to control particle size is found, for example, but not limitation, in paragraphs [0062]-[0065], [0069], [0103], [0109][0118-0127], and [0138].

#### **The Rejection under 35 U.S.C. §102(e)**

The Examiner rejected Claims 1, 4, 12, 14, 15, 18-20, 23-30, 34, 36, 44, 45, 54-57, 65, 124, and 131 under 35 U.S.C. §102(e) as being anticipated by Kessler et al. (6,095,153). In support of this rejection, the Office Action stated that "Kessler teaches a method for generating an aerosol comprising the steps of heating a physiologically active compound to vaporize the compound . . . and mixing the resulting vapor with a gas (air) in a ratio . . . to form a desired particle size when a stable concentration

of particles in the gas is reached; wherein the ratio of vapor to gas is controlled by regulating the rate of vaporization . . . ” Office Action at page 2-3. The Office Action further states that Kessler discloses among other things, mixing to prevent increase in gas temperature, and deposition of a thin film. *Id.* at 3.

Applicants appreciate the Examiner’s careful review of the references, but are confused with some of the purported disclosures in the Kessler reference. Kessler does not teach, disclose, or make obvious the elements of independent Claims 1, 54, 55, 56, 65, 124 and 131. These claims are all directed to either methods of generating an aerosol or delivering an aerosol to a patient. One element noticeably absent in the Kessler reference and explicitly stated in all these claims is that the vapor formed from heating a physiologically active compound is “mixed . . . with a gas, in a ratio, to form a desired particle size when a stable concentration of particles in the gas is reached . . . ” . Kessler does not discuss or mention “desired particle sizes.” Kessler does not mention or disclose “a stable concentration of particles in a gas.” Kessler does not mention or discuss “mixing a vapor in a gas in a ratio.” And finally Kessler does not discuss “mixing the vapor and gas in a ratio to form a desired particle size,” when a specified condition “stable concentration of particles” is reached.

The Office Action states that Kessler teaches “mixing the resulting vapor with a gas (air) in a ratio (via air inlet 29; col. 6, lines 64-67) to form a desired particle size when a stable concentration of particles in the gas is reached . . . “ *Id.* Applicants respectfully disagree. Kessler does teach use of an air inlet but does not state any such purpose. Rather Kessler states “The heating device 12 further includes an air inlet 29 for receiving air, either from the atmosphere or from an air pump (not shown) generally located within control module 16.” (U.S. Patent No. 6,095,153, col. 6 lines 64-68.) Mention of “mixing in a ratio to form a desired particle size when a stable concentration of particles in the gas is reached” is noticeably absent from this cite. Applicants request that the Examiner point to a particular portion of the reference that explicitly discloses this element. The Office Action itself notes that Kessler is silent with regards to the particle size in the range of 10 nm to 3 microns. (Office Action at 4) However, Applicants note that Kessler is completely silent about particle size.

The formation of any specifically desired particle size is not an inherent consequence of merely having gas flow. It is critical that that a proper ratio between the gas flow and the amount of vaporized compound be maintained in order to control the particle size to a particular size, and hence make a desired particle size. Kessler does not disclose directly or inherently manipulating or adjusting the ratio of gas flow and amount of vapor to control the particle size.

Anticipation requires that “a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter.” *PPG Industries, Inc. v. Guardian*

*Industries Corp.*, 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1642 (Fed. Cir. 1996), *see also* MPEP §2131 citing *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051 (Fed. Cir. 1987). As Kessler fails to disclose mixing in a ratio, to form a desired particle size when a stable concentration of particles in the gas is reached, the reference can not be said to anticipate the aerosol of Claims 1, 54, 55, 56, 65, 124 and 131. As Claims 4, 12, 14, 15, 18-20, 23-30, 34, 36, 44, 45 depend from Claim 1, and Claim 57 depends from Claim 56, these claims are not anticipated for the same reasons. Accordingly, the Applicants respectfully request that the Examiner reconsider and withdraw the rejection of these claims under 35 U.S.C §102(e).

### **The Rejections under 35 U.S.C. §103**

The Examiner rejected Claims 16, 17, 21, 22, 46, 47, 128-130 and 132-134 under 35 U.S.C. §103 as being unpatentable over Kessler et al. Office Action at page 4.

Specifically, with regard to Claims 16, 17, 46 and 47, the Office Action states that Kessler is silent with regard to particle size in the range of 10 nm to 3 micron. *Id.* The Office continues by stating it would have been obvious for one of skill in the art at the time of the invention to make the recited particle size in those ranges. *Id.* The Office Action, cites *in re Aller*, 104 USPQ 233 in support. *Id.* The court noted however, in upholding *in re Aller*, that Aller failed to teach the criticality of claimed ranges. Unlike Kessler, not only did Applicants teach specific ranges, e.g., 1 to 3 microns, and 10 to 100 nanometers, but also the criticality of those ranges. See US 2003/0062042A1 at [0017]. Also, Kessler fails, as discussed above, to recite the claim element “mixing in a ratio to form a desired particle size when a stable concentration of particles in the gas is reached.” According to the MPEP § 2143, “to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations.” Obviousness cannot be established by combining teachings in the prior art, absent some teaching or suggestion in the prior art that the combination be made (*In re Stencel* 828 F. 2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987); *In re Newell* 891 F. 2d 899, 13 USPQ2d 1248 (Fed. Cir. 1989)). Thus, the Office Action fails to state a prima facie case of obviousness.

Similarly with regard to claims 21 and 22, and claims 129 and 130, the Office Action notes that Kessler is silent with regards to the period of time in the recited range of the claims. But then states that it would have been a mere matter of design choice to have the time period be in a selected range which

could be attained through observation and experimentation or would have been obvious to optimize as it involves only routine skill in the art. See, Office Action at 4.

Applicants respectfully disagree. Again, Applicants state the criticality of the time range for heating as it impacts the rate of vaporization, the desired particle size, and amount of decomposition to be obtained and explicitly recites various times and time ranges that allow one to attain particles sizes in the ranges desired. See, e.g., US 2003/0062042A1 at [0120, 0121, 0123, 0128, 0138]. Moreover, Kessler teaches away from the ranges claims by Applicants. Kessler teaches using only exposure times to elevated temperatures wherein the “minimum exposure time is determined by the biomechanics of inhalation” and generally will “vary from about 3 to about 10-15 seconds.” US Patent No. 6, 095, 153 col. 8, lines 63-67. Thus the minimum range value disclosed by Kessler exceeds the maximum ranges claimed by Applicants and therefore could not render obvious the ranges claimed by the Applicants. Additionally, as was noted above, the limitation, “mixing in a ratio to form a desired particle size when a stable concentration of particles in the gas is reached,” is absent from Kessler and therefore could not render obvious dependent claims which also have this limitation.

Likewise, with regard to claims 128 and 132-134 the Office Action states that while Kessler is “silent with regards to high current stop being supplied by discharging a capacitor” . . . “it would have been obvious to one of skill in the art . . . as it is well known in the art to use capacitors or high current elements as heaters” and “it is well known in the art to use vaporize to provide mist to a user’s eye, skin or mucousa and would have been obvious to one of skill in the art.” Office Action at 4-5. Again, as these claims depend from independent claims that have the limitation “mixing in a ratio to form a desired particle size when a stable concentration of particles in the gas is reached” which is not disclosed in Kessler, a prima facie case of obviousness has not been presented. Moreover, this supposition is merely hindsight and no references were cited to support such a contention. Applicants request that references be cited or that the Examiner submit a declaration in support.

The Office Action rejected Claims 2, 3, 5, 7-10 under 35 U.S.C. 103(a) as being unpatentable over Kessler et al. in view of US 5,918,595 to Olsson et al. *Id.* at 5. Regarding Claims 2, 5 and 10, the Office Action states that Kessler is silent with regards to regulating the ratio of the vapor to gas by controlling the flow rate of the gas, but that as Olsson teaches a vaporizer in which the gas flow rate is regulated to control the delivery of the vapor along with the gas, it would be obvious to regulate the flow of gas to vary the ratio of vaporized medicament to gas. *Id.*

Applicants respectfully disagree. As was stated above, Kessler does not discuss or mention “desired particle sizes.” Kessler does not mention or disclose “a stable concentration of particles in a

gas.” Kessler does not mention or discuss “mixing a vapor in a gas in a ratio.” And finally Kessler does not discuss “mixing the vapor and gas in a ratio to form a desired particle size,” when a specified condition “stable concentration of particles” is reached. Additionally, as was noted by the Examiner, Kessler does not discuss regulating the ratio of vapor and gas by controlling the flow of gas. *Id.* Olsson does not cure these deficiencies or make obvious in view of Kessler how to accomplish these tasks. Olsson is not directed to aerosols, but rather to a method for vaporizing an anesthetic liquid in a carrier gas and making it available to mix with “other gas components to form a breathing gas.” US Patent 5,918,595, col. 1, lines 8-15. The breathing gas is not described as an aerosol of carrier gas and drug particles but rather is defined as consisting of “anesthetic gas” *Id.* at col. 2, lines 32-36. Additionally, the regulation of gas flow in Olsson is not directed to ratio of gas to vapor as a means to form a desired particle size, as disclosed in Applicants application, but is rather used to overcome the problem of most types of anesthetic vaporized which “is a lack of accurate control of the amount of anesthetic liquid vaporized” that affects the final concentration of anesthetic gas in the breath gas. *Id.* at col. 2, lines 32-36 and col. Olsson is providing a means “for maintaining a predetermined concentration of said anesthetic in said breathing gas.” *Id.* at col. 6, lines 37-42. Thus, the Office Action fails to establish even a *prima facie* case of obviousness as each and every element of the invention is not taught or disclosed by these references. Moreover for the same reason, there would be no motivation to combine the references to achieve the presently claimed invention, nor is it seen how the combination of the two references would achieve the presently claimed invention.

The Office Action states as to claims 3 and 7, that “Kessler teaches the step for regulating the rate of vaporization (by removing the delivery means 14 to limit further vaporization, col. 5, line 63-66.)” Office Action at 5.

Applicants respectfully disagree. Regulating the rate of an activity is not equivalent to turning on and off that activity. Rate may be defined as the speed or velocity. Kessler makes clear that the intent was not to change a rate of vaporization, but to control whether vaporization was to occur or not. (“After each inhalation, the user is able to remove the source material delivery means 14 from the heating device 12 so that **additional vaporization does not occur** until the delivery means 14 is reinserted.” US Patent No. 6,095,153, lines 63-66, emphasis added.). Moreover, as discussed throughout this response, Kessler fails to teach a ratio of gas to vapor to form a desired particle size. Applicants claims 3 and 7 were directed to using the rate of vaporization to control this ratio. As Kessler fail to teach each and every element of the invention, there can be no *prima facie* case of obviousness.

Regarding claims 8 and 9, the Office Action states that “Kessler teaches that the vaporization rate is controlled by manipulating the temperature.” Office Action at 5.

Applicants respectfully disagree and request a cite to a specific part of the reference that supports this contention. Kessler discloses that “to obtain vaporization of a given substance while avoiding combustion or denaturation of substances in the device, the operating temperature of the device . . . must be maintained within a very narrow range.” US Patent No. 6,095,153, col. 8, lines 47-50. Kessler does not disclose “controlling the vaporization rate by changing the energy transferred to the compound” which in turn controls “the ratio of vapor to gas,” in order to “form a desired particle size,” as Applicants have claimed in claims 8 and 9. Again, Kessler fails to teach or suggest all the claim limitations and thus fails to make obvious Applicants’ invention.

The Office Action rejected claims 6, 11, 13 under 35 USC 103(a) as being unpatentable over Kessler et al. in view of Olsson et al.(U.S. Patent No. 5,918,595) and in further view of Thwaites et al. (U.S. Patent No. 5,592, 934). According to the Office Action, while Kessler/Olsson is silent with regards to an annunciating signal, Thwaites teaches an alarm to alert a patient and thus it would be obvious to add the alarm of Thwaites to Kessler/Olsson. Office Action at 6. Also, the Office Action states that as to Claim 13, Kessler teaches stopping the compound from being vaporized. *Id.*

Applicants disagree. Thwaites like Olsson is not directed to an aerosol. Thwaites is to a vaporizer for delivering gaseous anesthetics. Thwaites, in describing his device, states explicitly “and an outlet 2 for a controlled mixture of carrier gas and gaseous anesthetic agent.” U.S. Patent No. 5, 592,932 col. 4, line 18-20. Thus, like Olsson there would be no motivation to combine Thwaites with Kessler. Additionally, Thwaites like Kessler and Olsson fails to disclose “controlling the vaporization rate by changing the energy transferred to the compound” which in turn controls “the ratio of vapor to gas,” in order to “form a desired particle size.” Thus, Thwaites does not overcome the limitation of Kessler and Olsson teaching or suggesting all the claim limitations and thus does not make obvious Claims 6 and 11. Regarding Claim 13, Applicants are confused as to how “stopping the compound from being vaporized” (Office Action at 6) by manually removing separating the material container portion of the device from the heater portion, makes obvious the element of “wherein the ratio of vapor to gas is controlled by regulating the gas flow to a maximum flow rate and stopping the compound from being vaporized in step (a) if the minimum flow rate is not maintained.” Kessler says nothing about the stopping the compound from being vaporized if a minimum flow rate is not maintained. Thus, Kessler does not suggest all the claims limitations of Claim 13. Additionally, Kessler as discussed above fails to contain the limitations of Claim 1 from which Claim 13 is a dependent claims and thus fails to make Claim 13 obvious.

The Office Action rejected Claims 31-33, 35, 37, 28 and 125-127 under 35 USC 103(a) as being unpatentable over Kessler et al in view of Wang (US 5,366,770). *Id.* According to the Office Action, although Kessler is silent with regard to heating a compound by heating a substrate through and alternating magnetic field, Wang teaches a vaporizer using a magnetic field and thus it would be obvious to use the heating step of Wang. *Id.*

Applicants respectfully disagree. Wang teaches away from the Applicant's invention. Wang is directed to formation of a plasma for coating a substrate. A plasma is formed from a gas when it is heated until the atoms loose all their electrons, leaving a highly electrified collection of nuclei and free electrons. During the process, Wang transiently forms an aerosol but not from the heating step described in the Office Action. Rather the aerosol or mist, as Wang describes it, is formed using an ultrasonic nebulizer. (U.S. Patent No. 5,366,770, col. 3, lines 3-39.) The aerosol is then transferred into a plasma reactor where it is mixed with plasma gas and subjected to radio frequency radiation "to cause the plasma gas to react with the mist" to generate a plasma for coating a substrate. *Id.* column 3, lines 57-66. Wang is heating the material to form a plasma, whereas Applicants are heating a substrate by generating an alternating current in the substrate material to vaporize a compound from the substrate that upon mixing with the gas forms aerosol particles of a desired particle size. One of skill in the art would not use the heating of Wang in place of Applicants for purposes of carrying out the invention. Applicants' invention is directed to minimizing decomposition and one would want to minimize any reactions of the compound with other reagents, whereas heating to form a plasma, as described by Wang causes disruption of the basic atom itself. Thus, there would also be no motivation to combine Wang with Kessler for the same reason. Moreover, Wang does not overcome any of the limitations of Kessler, in that Wang also does not disclose or suggest, "mixing the resulting vapor with a gas, in a ratio, to form a desired particle size when a stable concentration of particles in the gas is reached." For these reasons, there can be no *prima facie* case of obviousness.

The Office Action rejected claims 32-33 and 125-127 as obvious in view of Wang, stating it teaches the use of mesh, metallic, stainless steel foil (col.6, lines 51-54.).

Applicants respectfully disagree. Wang in describing an electronic cell on which a plasma will be coated states "it will be seen electronic cell unit 60 may first be formed as a substantially flat sheet (see FIG.3) and then rolled into a tubular shape to form tube 61 (see FIG. 4)." US Patent 5,366,770 col. 6, lines 51-54.). Applicants are confused as to any discussion of the use of a mesh, metallic, stainless steel foil in this section. Moreover, nowhere in Wang is the metallic material, which is defined in lines 54-58 as being only a nickel-containing substrate, described or used as a substrate upon which is coated a physiological compound which is then heated to vaporize the compound with a desired particle size for delivery to a



patient. Rather the substrate in Wang is the material on which the plasma is deposited. The materials disclosed are not the same or for the same or similar uses. Thus, there would be no motivation to use the materials in Wang in the instant application. Moreover, as stated above, Wang is also deficient in failing to disclose or suggest "controlling the vaporization rate by changing the energy transferred to the compound" which in turn controls "the ratio of vapor to gas," in order to "form a desired particle size."

As to claim 35, the Office Action states that Kessler and Wang are silent as to the thickness of the deposited compound, but that it would be obvious to one of ordinary skill to have the thickness in the recited range, because it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. Office Action at 7.

Applicants agree that both Kessler and Wang are silent as to the thickness, but disagree that it would be obvious in view of *In re Aller*. *In re Aller* involved optimization within a disclosed range already in the art. The Examiner has not cited to any ranges being disclosed or discussed in the art. Thus, this is not analogous to *In re Aller*. Applicants' invention is directed to making physiologically active compounds that have low decomposition and a desirable particle size for deposition. To accomplish this requires addressing a variety of factors as disclosed in the instant application. See US 2003/0062042 A1 [0119]-[0127]. One factor in particular is raising the compound to the maximum temperature for a minimum duration of time to minimize decomposition. *Id.* at [0121] and [0123]. One method of accomplishing this, as described in the instant application, was to coat the physiologically active material at a thickness of less than 10 microns. *Id.* at [0140]. Neither Kessler nor Wang disclose or suggest using a film of a specific thickness to accomplish these tasks. Moreover, Wang does not even use a material that could be coated in that Wang is aerosolizing a solution.

The Office Action rejected claims 37 and 38 as being obvious in view of Wang. According to the Office Action, Wang teaches the field maintained at 1 MHz, but is silent with regards to 200-300 kHz, however, it would be obvious to have the field (presumable intended as opposed to "thickness" as stated) in that range, as general conditions were disclosed in the prior art. See Office Action at 7.

Applicants respectfully disagree. Wang uses these frequencies for the purpose of generating a plasma from an aerosol. (See US Patent 5,366,770 "Radio frequency energy is applied to the reagents in the plasma reactor 24, and it causes vaporization of the mist." Col. 4, lines 45-47.) Applicants are using the frequency to create a field which was designed to work with the electronics of the system and heat the substrate sufficiently to vaporize a drug. Optimization of frequency ranges for the purpose of generating a plasma is not the same as optimizing to effectively generate an electric current to heat a substrate to vaporize a physiologically active compound from the substrate. Thus, there would be no motivation to

combine Wang with Kessler and no motivation to optimize the frequency used in Wang in a system to volatilize a coated material from a substrate through effective heating of the substrate.

Accordingly, and in light of the foregoing arguments, the Applicants respectfully request that the Examiner reconsider and withdraw all rejections based on 35 U.S.C §103

### **Conclusion**

The Applicants appreciate the Examiner's careful and thorough review of the application and submit that the Examiner's concerns have been addressed by the amendments and remarks above. The Applicants accordingly request the Examiner to withdraw all rejections and allow the application. In the event the Examiner believes a telephonic discussion would expedite allowance or help to resolve outstanding issues, prosecution of the application, then the Examiner is invited to call the undersigned at (650) 687-3905. Please direct all correspondence to the following customer number: 37485.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that a further extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 502731.**

Respectfully submitted,



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